DEPARTMENT OF HEALTH & HUMAN SERVICES

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National Cancer Institute
Bethesda, Maryland 20205

Dr. Purnell W. Choppin
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Dear Dr. Choppin:

I thank you very much for your letter on behalf of the search committee considering individuals for a senior position as a laboratory head at the Rockefeller University. I do indeed have a possible interest in being considered for such a position by the committee. I have never responded positively to inquiries from similar search committees for other positions. I had assumed that I would stay at the NIH throughout my research career. However, certain recent trends have made me reconsider this issue. Although our Branch received an outstanding rating in our project site visit headed by Dr. Matthew Scharff, Dr. Jack Stobo, and Dr. Harold Varmus, our Branch is in the Division of Cancer Biology and Diagnosis of the Cancer Institute, and it is clear that this broad division will have a marked cut in its personnel ceiling. The Cancer Institute is approximately 300 billets above its limit and may have an additional cut of 588 positions. A disproportionate number of such cuts will be in the Division of Cancer Biology and Diagnosis. We are at this time in a hiring freeze so that we cannot replace individuals who leave the NIH. In the future it appears that this division will be limited to replacing one individual for every 2-1/2 that leave. Even these projections assume no cuts in the NIH personnel ceiling by the present administration. Thus, my decision concerning leaving the NIH would be affected in part By events here at the NIH during the next few weeks as well as the opportunities for research at the Rockefeller University.

I am enclosing a copy of my curriculum vitae and bibliography as you requested. In addition, I am enclosing an overview of my own individual research program, an abstract of a presentation to our board of scientific advisers, and a copy of an outline of future plans for myself and my associate, Dr. Warner Greene, related to this abstract. Our general goals and future plans for research include major efforts in the following areas:

(1) Continued studies on interleukin-2 receptors on normal and malignant T cells. As outlined on the accompanying sheets, we are interested in the molecular biology of the genes encoding the IL-2 receptor. The regulatory control of such IL-2 receptor gene expression, especially that associated with HTLV-1, transformed human T cells. We are examining the possibility that the HTLV-1 encoded LOR protein acts

on the regulatory regions of the IL-2 receptor inducing its expression. I am also very interested in the functional role of IL-2 and its receptor in controlling T-cell and B-cell function. Finally, we are interested in using the anti-Tac monoclonal antibody that identifies the IL-2 receptor expressed on certain leukemic T cells and activated normal T cells in the therapy of patients with adult T-cell leukemia. In these studies we plan to use both unmodified anti-Tac as well as conjugates of anti-Tac with ricin A, Pseudomonas toxin and the alpha-emitting isotope of bismuth. Studies on the therapy of patients with T-cell leukemia have been initiated. In addition, we plan in the future to examine the effect of anti-Tac in protocols involving organ transplantation.

(2) An additional area of major interest is the analysis of the arrangement of immunoglobulin genes and the genes encoding the alpha and beta chain of the antigen-specific T-cell receptor and the rearrangements and deletions of these genes involved in the control of immunoglobulin synthesis and the generation of receptors on effector T cells. Recombinant DNA technology involving analysis of immunoglobulin and T-cell receptor genes is being used to classify neoplasms of the B and T cell series and to establish their clonality. We are using these approaches to define the state of differentiation of neoplastic B-cell and T-cell precursors and to determine the mechanisms that lead to failure of maturation of such cells. Recently we have been emphasizing studies utilizing probes to the T-beta, T-alpha and T-gamma receptor genes of humans.

(3) A major additional interest has been in the functional capacity of B cells and immunoregulatory cells including helper T cells, suppressor T cells and monocytes that regulate the normal antibody responses, and on the studies of leukemias of immunoregulatory cells, and of disorders of immunoregulatory cell interactions in patients with immunodeficiency diseases. Using <u>in vitro</u> assay systems, we were the first to demonstrate disorders of such cells in a subset of patients with common variable immunodeficiency disease, in patients with thymoma- and hypogammaglobulinemia as well as to demonstrate class-specific suppressor cells in patients with selective IgA deficiency and monocytes that act as polyclonal suppressors in patients with multiple myeloma. Our goals in this area are to define the molecular basis for the suppressor event. We are attempting to isolate and characterize a lymphokine that inhibits B-cell but not T-cell function. Initially we focused on T cell lines and T-T cell hybridomas as the source of this lymphokine; more recently we have been utilizing cell lines established with the virus HTLV-1 that constitutively secretes this lymphokine but that are no longer productive of virus, therefore appearing to be a safe source of material for both purification of the lymphokine and molecularly cloning the gene encoding this factor. We are also interested in immunotherapeutic approaches that might diminish suppressor T cell action and thus may be of value

in reversing the immunodeficiency of subsets of patients with immunodeficiency diseases and an excessive number of activated suppressor T cells.

I thank you again for considering me for a senior position as a laboratory head at the Rockefeller University.

Yours sincerely,

Dr. Thomas A. Waldmann
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